PCT/EP00/07358

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Bescheinigung | Certificate | Attestation

EP 00/07358

4

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99126035.7

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Anmeldetag
Date of filing
Date de dépôt
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Titre de l'invention
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NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

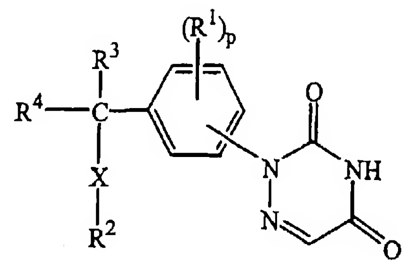
The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

US 4,631,278 discloses α-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of the production of IL-5.

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or-X-R^2 taken together may represent cyano;

Y represents O, S, NR^5, or $S(O)_2$;

each R^1 independently represents C(=0)·Z-R^{14}, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with C(=0)-Z·R^{14}, Het^3, R^6 or NR^7R^8;

R^2 represents Het^1, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from C(=0)·Z-R^{14}, hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14} , arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

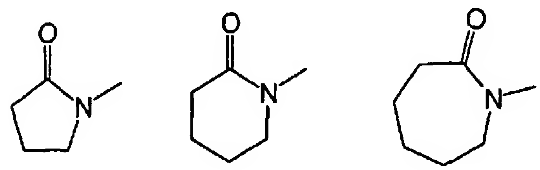
R^4 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6}alkanediyl;

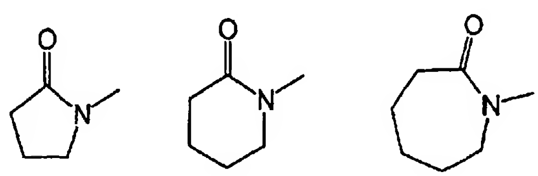
R^5 represents hydrogen or C_{1-4}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, piperidinylsulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, arylcarbonyl, Het^{3}carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^{3}aminocarbonyl, Het^{3}aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6; or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a radical of formula

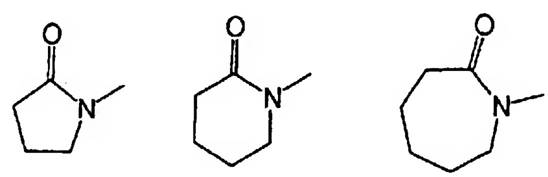


R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, Het^{3}carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^{3}aminocarbonyl, Het^{3}aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6; or R^9 and R^{10} taken together with the nitrogen atom to which they are attached form a radical of formula

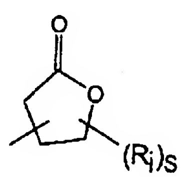


each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy optionally substituted with C(=0)-Z-R^{14}, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)$NR^{15}R^{16}$, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, C_{3-7}cycloalkyloxy optionally substituted with C(=0)-Z-R^{14}, phthalimide-2-yl, Het^3 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} and R^6; or R^{12} and R^{13} taken together with the nitrogen atom to which they are attached form a radical of formula



each R^{14} independently represents hydrogen, C_{1-20}acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20}alkyl, C_{3-20}alkenyl optionally substituted with phenyl, C_{3-20}alkynyl, C_{3-7} cycloalkyl, polyhaloC_{1-20}alkyl, Het^5, phenyl or C_{1-20} alkyl substituted with one or more substituents selected from hydroxy, $NR^{17}R^{18}$, phenyl, mono- or di-(C_{1-4}alkyl)amino, cyano, Het^5, C_{1-4} alkyloxycarbonyl, phenyl C_{1-4} alkyloxycarbonyl and C_{3-7} cycloalkyl, or R^{14} represents a radical of formula



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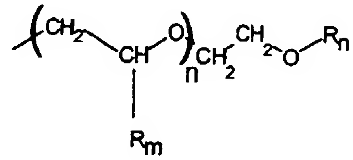

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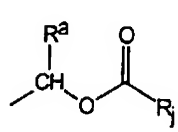

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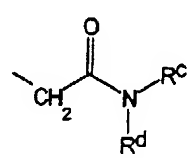

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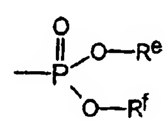

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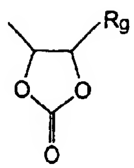

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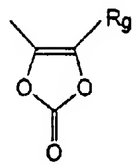

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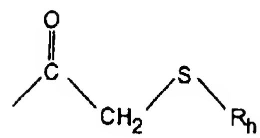

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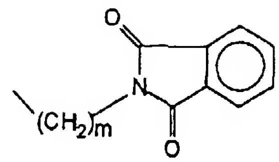

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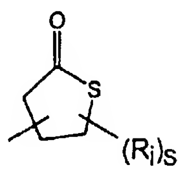

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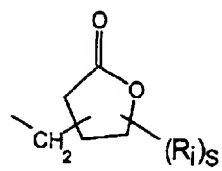

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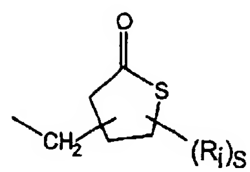

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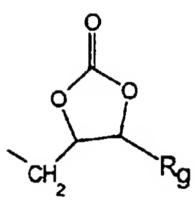

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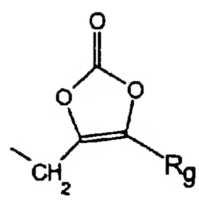

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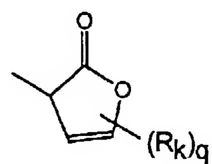

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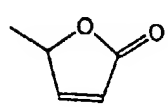

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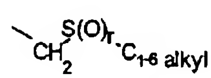

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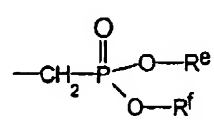


(t)

wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;

R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C_{1-6}alkyl, phenyl or C_{3-7}cycloalkyl; or

R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;

R_g, R_h and R_k are each independently hydrogen or C_{1-4} alkyl

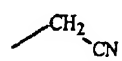
R_i is C_{1-4}alkyl;

R_j is -O-R_b, C_{1-6}alkyl, phenyl or C_{3-7}cycloalkyl optionally substituted with C_{1-4} alkyloxy;

where R_m is hydrogen or C_{1-4} alkyloxy and R_n is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, phenyl or phenylC_{1-4}alkyl

each Z independently represents O, S, NH, -CH_2-O- or -CH_2-S- whereby -CH_2- is attached to the carbonyl group; or

-Z-R^{14} taken together form a radical of formula



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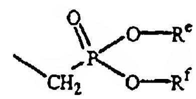
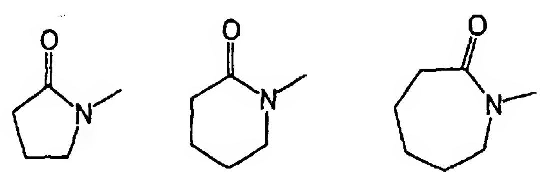


(g)

R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, -C(=O)-Z-R^{14}, arylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, aminocarbonylmethylene, mono- or di(C_{1-4}alkyl) aminocarbonylmethylene, Het^3aminocarbonyl, Het^3aminothiocarbonyl, pyridinylC_{1-4}alkyl, Het^3 or R^6; or R^{15} and R^{16} taken together with the nitrogen atom to which they are attached form a radical of formula



R^{17} and R^{18} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl, -C(=O)-Z-C_{1-6}alkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl and R^6;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, C(=O)NR^9R^{10}, C(=O)-Z-R^{14}, R^6, -O-R^6, phenyl, Het^3, C(=O)Het^3 and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3 or NR^9R^{10};

Het[1] represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het[2], R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het[2] and R^{11};

Het[2] represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het[4], R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het[4] and R^{11};

Het[3] represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-Z-R^{14}, R^{6} and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, R^{6} and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

Het^5 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{17}R^{18}$, C(=O)-Z-C_{1-6}alkyl, R^6, sulfonamido and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-C_{1-6}alkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl, R^6 and $NR^{17}R^{18}$;

provided however that

- R^2 is other than C_{1-6} alkyloxycarbonylC_{1-6}alkyl or aminocarbonyl; and
- R^7, R^8, R^9 and R^{10} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, C(=O)-O-R^{19}, C_{1-4}alkanediylC(=O)-O-R^{19} or –Y-C_{1-4}alkanediylC(=O)-O-R^{19}; and
- R^{12} and R^{13} are other than C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkylcarbonylcarbonyl; and
- R^{11} is other than C(=O)-O-R^{19}, Y-C_{1-4}alkanediyl – C(=O)-OR^{19}, C(=O)NH_2, C(=O)NHC_{1-4}alkyl or C(=O)NHC_{3-7}cycloalkyl; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkyloxycarbonylcarbonyl; and
- aryl is other than phenyl substituted with C(=O)-O-R^{19}, C(=O)NH_2, C(=O)NHC_{1-4}alkyl, C(=O)NHC_{3-7}cycloalkyl and/or with C_{1-4}alkyl substituted with

$C(=O)-O-R^{19}$ or Y-C_{1-4}alkanediyl – $C(=O)-O-R^{14}$; and

- Het^3 is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{19}$ and/or with C_{1-4}alkyl substituted with $C(=O)-O-R^{19}$ and/or Y-C_{1-4}alkanediyl – $(=O)-O-R^{19}$; and
- in each of the above proviso's R^{19} is defined as hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene or mono- or di(C_{1-4}alkyl)aminocarbonylmethylene; and

the said compound of formula (I) contains at least one – $C(=O)-Z-R^{14}$ moiety.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{1-20}alkyl is meant to include C_{1-6}alkyl and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like; C_{5-20}alkyl is meant to include C_{1-20}alkyl except for C_{1-4}alkyl; C_{3-20}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 20 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl and the like, the carbon atom of the said C_{3-20}alkenyl connected to the remainder of the molecule being preferably saturated; C_{3-20}alkynyl defines straight and branched chain hydrocarbon radicals containing one triple bond and having from 3 to 20 carbon atoms such as, for example, 2-propynyl, 3-butynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 3-methyl-2-butynyl, 3-hexynyl and the like, the carbon atom of the said C_{3-20}alkynyl connected to the remainder of the molecule being preferably saturated; polyhaloC_{1-4}alkyl is defined as polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl; polyhaloC_{1-20}alkyl is defined as polyhalosubstituted C_{1-20}alkyl. The term C_{1-4}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl

and the like; C_{2-6}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

Het^1, Het^2, Het^3 , Het^4 and Het^5 are meant to include all possible isomeric forms of the heterocycles mentioned in the above definitions, for instance pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

The heterocycles represented by Het^1, Het^2, Het^3, Het^4 and Het^5 may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzothiazolyl, it may be 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl and 7-benzothiazolyl.

The C_{1-20}acyl is derived from

acetic acid	CH_3COOH	tridecanoic acid	$C_{12}H_{25}COOH$
propionic acid	C_2H_5COOH	myristic acid	$C_{13}H_{27}COOH$
butyric acid	C_3H_7COOH	pentadecanoic acid	$C_{14}H_{29}COOH$
valeric acid	C_4H_9COOH	palmitic acid	$C_{15}H_{31}COOH$
hexanoic acid	$C_5H_{11}COOH$	heptadecanoic acid	$C_{16}H_{33}COOH$
heptanoic acid	$C_6H_{13}COOH$	stearic acid	$C_{17}H_{35}COOH$
octanoic acid	$C_7H_{15}COOH$	oleic acid	$C_{17}H_{33}COOH$
nonanoic acid	$C_8H_{17}COOH$	linolic acid	$C_{17}H_{31}COOH$
decanoic acid	$C_9H_{19}COOH$	linolenic acid	$C_{17}H_{29}COOH$
undecanoic acid	$C_{10}H_{21}COOH$	nonadecanoic acid	$C_{18}H_{37}COOH$
lauric acid	$C_{11}H_{23}COOH$	icosanoic acid	$C_{19}H_{39}COOH$

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form. The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het^1, Het^2, Het^3, Het^4 and Het^5 may be *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included

within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position. Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- X is S, NR^5 or a direct bond; more preferably a direct bond;
- each R^1 independently is halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- the at least one – $C(=O)-Z-R^{14}$ moiety contained by the compound of formula (I) is born by R^2,

- R^2 is Het^1 or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C(=0)-Z-R^{14} ,C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14}, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl; more preferably R^2 is Het^1 ;
- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl, more preferably methyl;
- R^4 is hydrogen or methyl, more preferably methyl;
- R^3 and R^4 are taken together to form a 1,4-butanediyl;
- R^6 is C_{1-6}alkylsulfonyl or aminosulfonyl;
- R^7 and R^8 are each independently hydrogen, C_{1-4}alkyl, Het^3 or R^6;
- R^9 and R^{10} are each independently hydrogen, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, Het^3carbonyl, Het^3 or R^6;
- R^{11} is cyano, nitro, halo, C_{1-4}alkyloxy, formyl, NR^7R^8, C(=O)$NR^{15}R^{16}$, -C(=O)-Z-R^{14}, aryl, arylcarbonyl, Het^3 or C(=O)Het^3; more preferably R^{11} is phenyl, -C(=O)-O-R^{14}, -C(=O)-S-R^{14} or -C(=O)-NH-R^{14}.
- R^{14} is dihydrofuranyl, C_{5-20}alkyl, C_{3-20}alkenyl, polyhaloC_{1-6}alkyl, Het^5 or C_{1-20}alkyl substituted with one or more substituents selected from phenyl, C_{1-4}alkylamino, cyano, Het^1 , hydroxy and C_{3-7}cycloalkyl;
- R^{17} and R^{18} are each independently hydrogen or phenyl;
- aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC1-4alkyl, NR^9R^{10}, C(=O)NR^9R^{10}, C(=O)-O-R^{14}, -O-R^6, phenyl, C(=O)Het^3 and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, C(=O)-Z-R^{14}, Het^3 and NR^9R^{10};
- Het^1 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted

with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}; more preferably Het^1 is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11};

- Het^2 is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl;
- Het^3 is piperidinyl, piperazinyl, morpholinyl or tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkylcarbonyl, piperidinyl and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy and phenyl;
- Het^4 is thienyl;
- Het^5 is piperidinyl or piperazinyl optionally substituted with C_{1-4}alkyl or sulfonamido.

Special compounds are those compounds of formula (I) wherein p is 2 and both R^1 substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

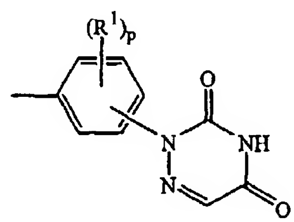
Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted

with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}; more in particular R^2 is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I) wherein R^3 and R^4 are both methyl and $-X-R^2$ is Het^1 wherein Het^1 suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

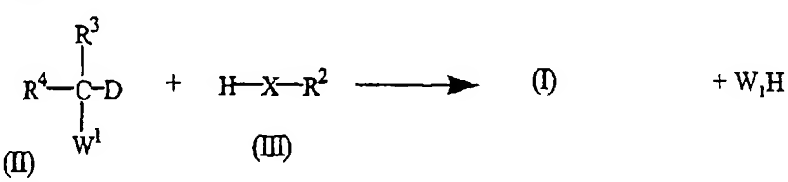
More preferred compounds are those compounds of formula (I) wherein R^3 and R^4 are both methyl, $-X-R^2$ is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents.

In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by a series of reactions comprising the step of reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



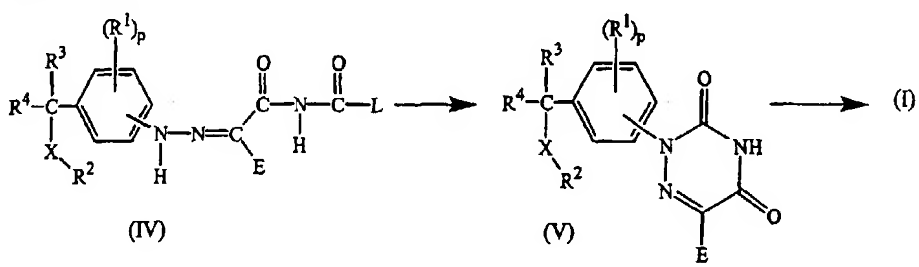
Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no

additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiumethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

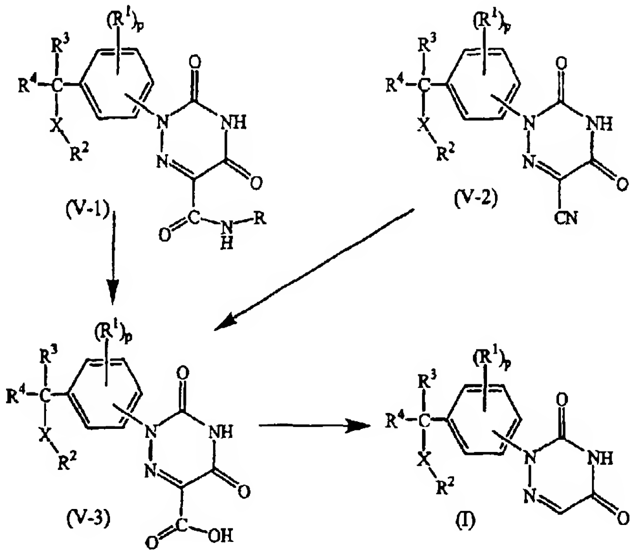
Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and WO99/02505.

Alternatively, for instance, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6}alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C_{1-6}alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.

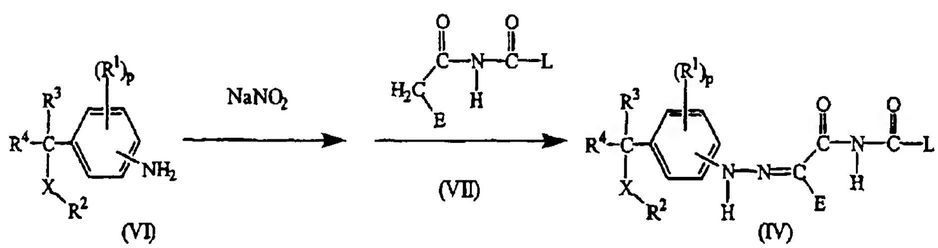


Depending on its nature, E can be eliminated using various art-known elimination procedures. For example when E is an amide or a cyano moiety, it can be hydrolized to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated

temperatures ranging up to reflux temperature.



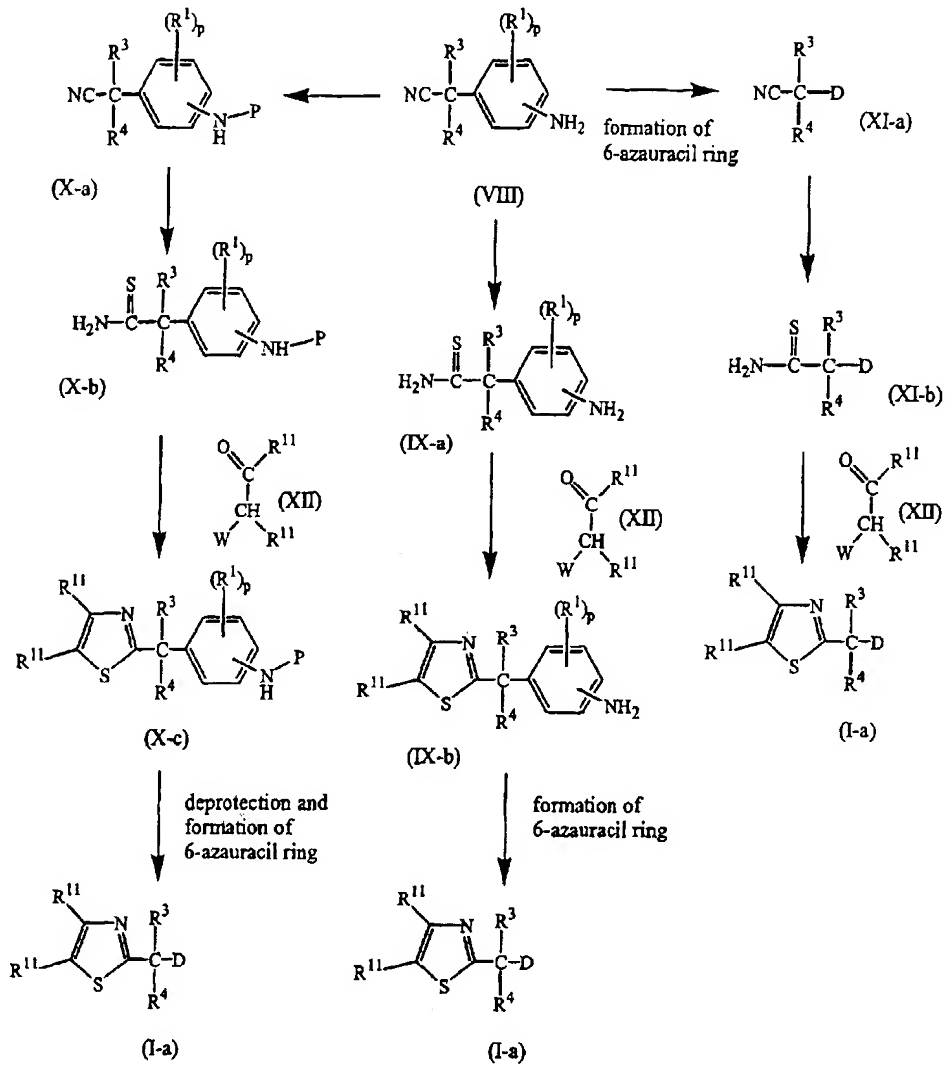
A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.



An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 above depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

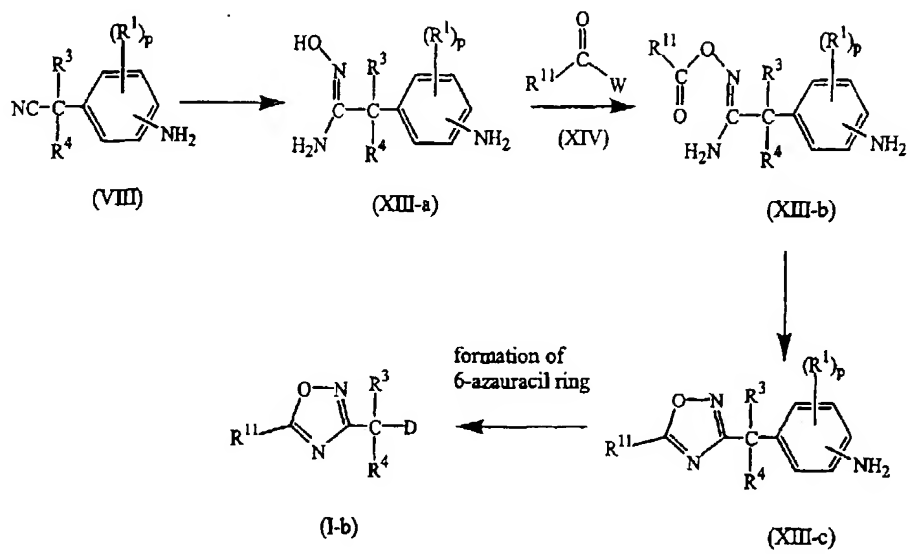
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H_2S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b-1) can be prepared by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

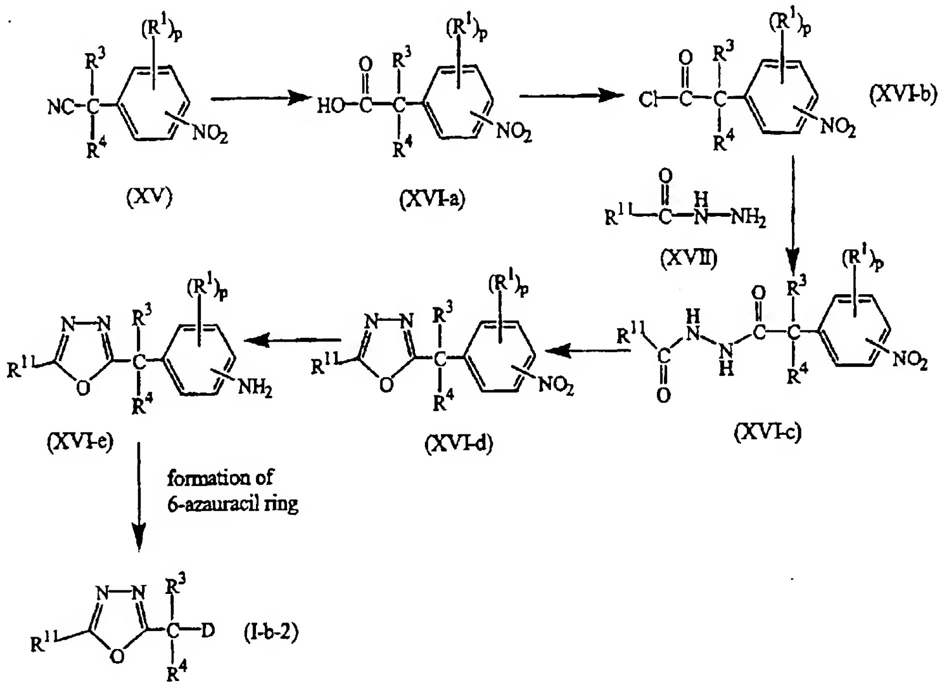


In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethaneamine. The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

Still another interestng subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

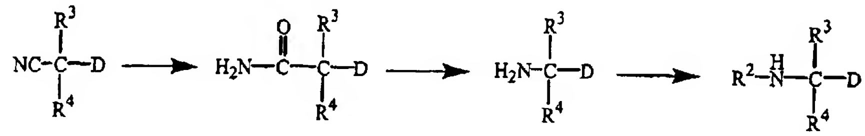
Scheme 3



The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid derivative of formula (XVI-a) may the further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N,N*-(1-methylethyl)ethaneamine. The thus formed intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phophoryl chloride.As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is -NH-R^2, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

Scheme 4

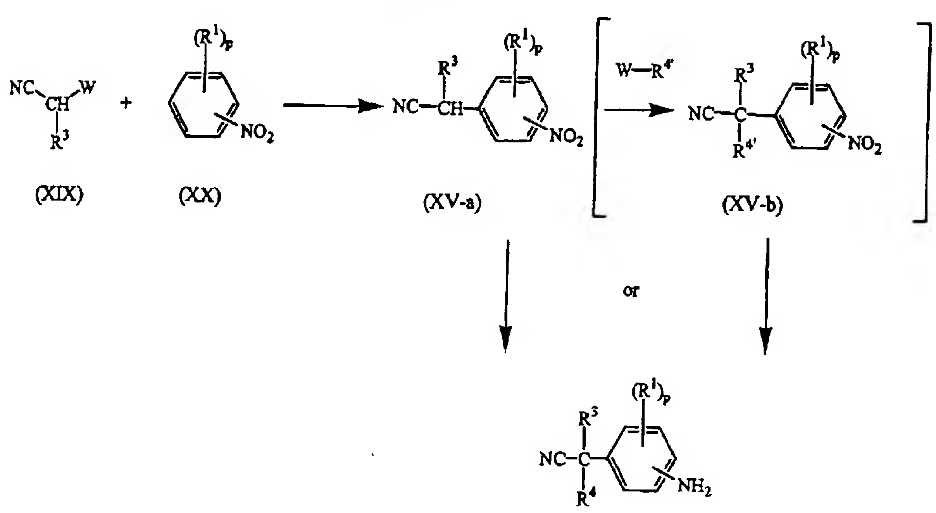


(XI-a) (XVIII-a) (XVIII-b) (I-c-1)

In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolized to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) p. 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5

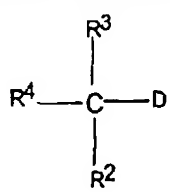


(VIII)

An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted

in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presnece of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula $R^{4'}$-W wherein $R^{4'}$ is the same as R^4 but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter. In particular, compounds of formula (I) containing at least one – C(=O)-Z-R^{14} moiety born by R^2, wherein Z is O or S and R^{14} is other than hydrogen, can suitably be prepared by reacting the compound of formula (XXI) containing the corresponding moiety – C(=O)-Z-H with an appropriate reagent of formula (XXII) wherein W^2 is a suitable leaving group, as follows:



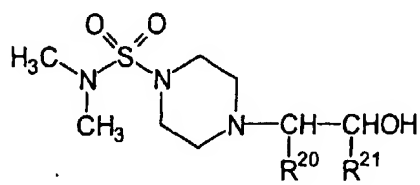
$+ W^2\text{-}R^{14} \longrightarrow$ (I) $+ W^2H$

(XXI) (XXII)

For instance a first process of such preparation involves reacting the compound of formula (XXI) containing the corresponding moiety – C(=O)-Z-H with a halide, preferably a bromide having the formula Br -R^{14}, in a reaction-inert solvent such as defined above and in the presence of sodium hydrogenocarbonate. The said reaction is performed at a temperature below the boiling point of the solvent used and, for example, for a period of time between about 2 and 18 hours when dimethylformamide is used as the solvent. A second process of such preparation involves reacting the compound of

formula (XXI) containing the corresponding moiety – C(=O)-Z-H with an alcohol having the formula R^{14}-OH, in a reaction-inert solvent such as defined above and in the presence of 1,1'-carbonylbis-1H-imidazole optionally admixed with 1,8-Diaza-7-bicyclo (5.4.0) undecene. When methylene chloride is used as the solvent, the reaction may be performed at room temperature for a period of time of several hours.

The present invention is also concerned with new compounds of formula :



(XXIII)

wherein R^{20} and R^{21} are each independently selected from hydrogen or C_{1-20} alkyl or R^{20} and R^{21} taken together with the carbon atom to which they are attached form a cycloalkyl radical. These new compounds are useful for preparing a compound of formula (I) when Het^5 represents a sulfonamido substituted piperazine. Such intermediate compounds of formula (XXIII) can be prepared by reacting N,N-dimethyl-1-piperazinesulfonamide with an alkylene oxide in a reaction-inert solvent such as methanol and/or methylene chloride. Suitable alkylene oxides for this purpose include for instance ethylene oxide, propylene oxide, 1-2 butylene oxide, cyclohexylene oxide and the like.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable

solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, *91*, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, Il-3, IL-4, IL-6, IL-10, γ-interferon (IFN-γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen, carbon

dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxy-C_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD

(2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S.value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C-atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^1 is a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I, ^{123}I, ^{125}I, ^{131}I; radioactive bromides, e.g. ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and radioactive fluorides, e.g. ^{18}F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radio-labelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

a) A mixture of 2-chloropropionitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (interm. 1).

b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N_2 flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N_2 flow for 1 hour. CH_3I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (interm. 2).

c) A mixture of intermediate (2) (0.066 mol) in CH_3OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H_2, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated, yielding 17.1g of 4-amino-2,6-dichloro-α,α-dimethylbenzene-acetonitrile (interm. 3).

Example A2

a) A solution of $NaNO_2$ (0.36 mol) in H_2O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH_2Cl_2, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl *N,N'*-[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propane-diyl]dicarbamate (interm. 4).

b) A solution of intermediate (4) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing ethyl [[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 5) was used as such in the next step.

c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

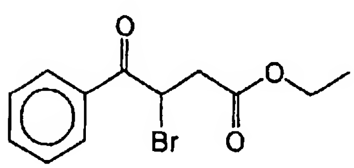
d) A suspension of intermediate (6) (0.28 mol) in mercaptoacetic acid (250.0 ml) was stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in

DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,α-dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,α-dimethylbenzeneacetonitrile (interm. 7).

e) A solution of intermediate (7) (0.107 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H_2S was allowed to bubble through this solution for 24 hours at 80°C. H_2S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated. CH_2Cl_2/CH_3OH (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4]-α,α-dimethylbenzeneethanethioamide (interm. 8).

Example A3

Reaction under N2 atmosphere. A solution of intermediate (8)(0.0125 mol) and



(0.0157 mol) in ethanol (60 ml) and DMF (30 ml; dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT. The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH_2Cl_2 (100 ml). The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, then 99/1, ending with 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH_3CN. The precipitate was filtered off, washed with CH_3CN and DIPE, then dried (vacuum, 50 °C), yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a

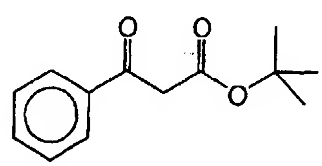
melting point of 148°C.

Example A4

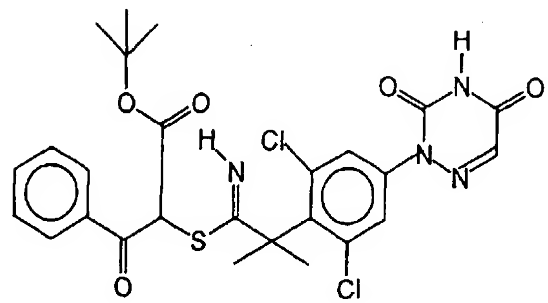
A mixture of intermediate (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH_3OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid (intermediate (10)).

Example A5

First a solution of bromine (0.02 mol) in CH_2Cl_2 (20 ml) was added dropwise at 10°C under N_2 flow to a mixture of a compound of formula

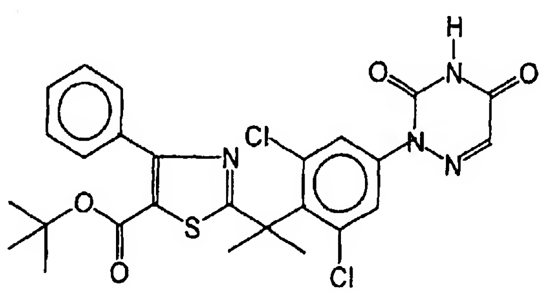


(0.0227 mol) in CH_2Cl_2 (50ml). The mixture was stirred at 10°C for 1 hour. H_2O and solid K_2CO_3 were added. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues yielding 14 g (51%) of 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mol), 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate (0.0137 mol) and K_2CO_3 (0.0357 mol) in CH_3CN (55ml) was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification. Yielding: 8g of intermediate 11 having the formula



Example A6

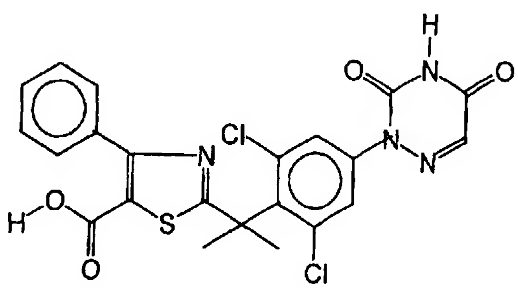
Intermediate (11) (0.0119 mol) and tert.-butanol (24g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm). Two fractions were collected and their solvents were evaporated. Yielding: 2.66g (fraction 1) and 0.7g fraction 2 (50%). Fraction 2 was purified by column chromatography over C 18 (eluent: CH_3OH/NH_4OAc 0.5% 80/20; column: HYPERSIL C 18 3 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.45g of intermediate 12 having a melting point of 130°C and represented by the formula



Example A7

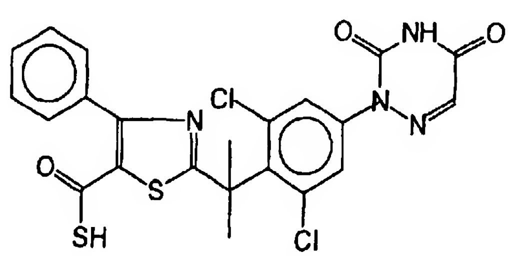
Intermediate 12 (0.00465 mol) was added portionwise at 0°C-10°C to trifluoroacetic acid (35ml). The mixture was stirred at room temperature for 3 hours and poured out into H_2O. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2.

The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried. Yielding: 1.16g of intermediate 13 having a melting point of 232°C and represented by the formula



Example A8

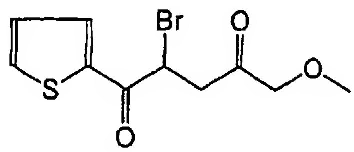
1,1'-carbonylbis-1H-imidazole (0.0159 mol) was added portionwise at RT under N_2 flow to a solution of intermediate (13) (0.00795 mol) in DMF (60 ml). The mixture was stirred at RT overnight. H_2S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a sarurated NaCl solution and extracted twice with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The product, interm.14 represented by the formula



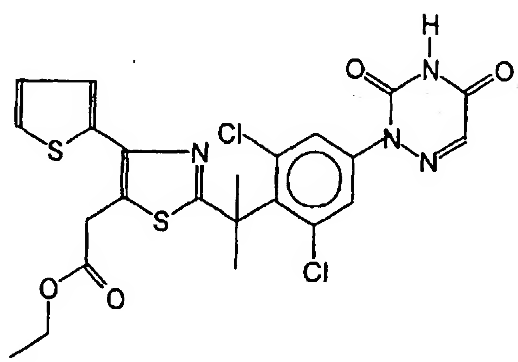
was used without further purification.

Example A9

A mixture of intermediate (8) (0.0158 mol) and



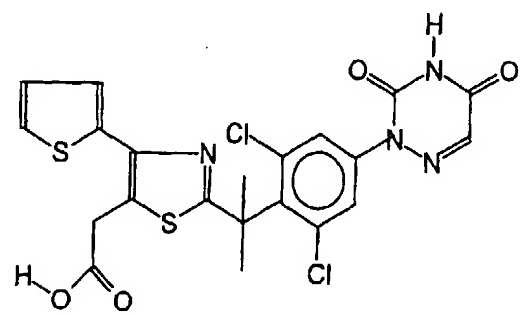
(0.0237 mol) in ethanol (60ml) and DMF (40ml) was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (11.2g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 4.2g (47%). Part of this fraction (1.5g) was crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula



Example A10

A mixture of intermediate (15) (0.0045 mol) and NaOH (0.0135 mol) in methanol (30ml) and THF (30ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1; 15-40

μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.5g (64%). Part of this fraction (1g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g of intermediate 16 having a melting point of 192°C and represented by the formula



Example A11

a) $NaOCH_3$ 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH_3OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g of (26%) 4-amino-2,6-dichloro-N'-hydroxy-α,α-dimethylbenzeneethanimidamide (interm. 17).

b) A solution of intermediate (17) (0.0323 mol) and *N,N*-bis(methylethyl)ethanamine (0.0339 mol) in CH_2Cl_2 (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidenyl]amino 2-methylbenzoate (interm. 18).

c) A solution of intermediate (18) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction

mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (interm. 19).

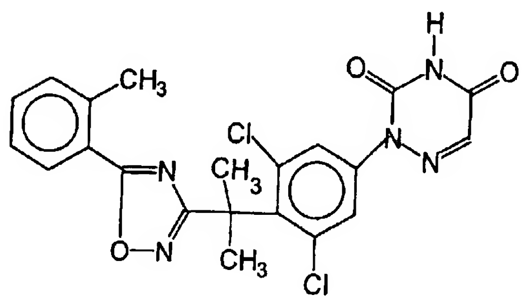
d) A solution of intermediate (19) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C. A solution of $NaNO_2$ (0.032 mol) in water (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding diethyl *N,N'*-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (interm. 20).

e) A solution of intermediate (20) (0.0302 mol) and sodium acetate (0.0302 mol) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methyl-phenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 21).

f) A mixture of intermediate (21) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 22).

Example A12

A mixture of intermediate (22) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 23 represented by the formula

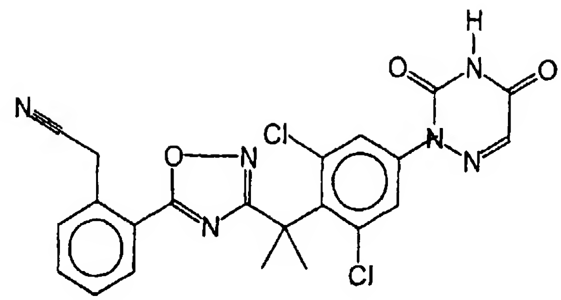


Example A13

A mixture of intermediate (23) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl_4 (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (intermediate 24).

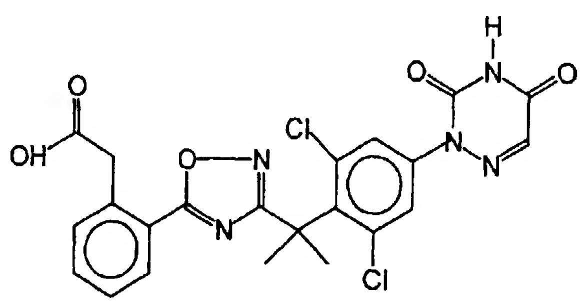
Example A14

A solution of intermediate (24) (0.017 mol) and KCN (0.034 mol) in ethanol (100 ml) and H_2O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH_2Cl_2, then washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 8.2 g of interm.25 represented by the formula



Example A15

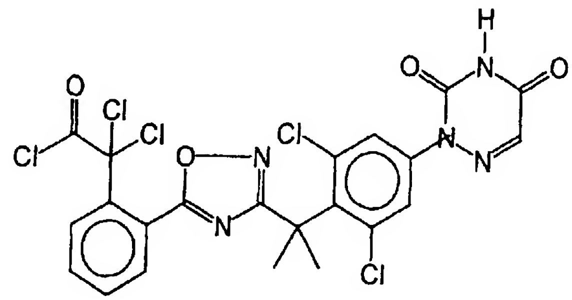
A solution of intermediate (25) (0.017 mol) in HOAc (50 ml), H_2SO_4 (50 ml) and H_2O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into ice-water and the resulting precipitate was filtered off, washed, then dissolved in CH_2Cl_2. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by high performance liquid chromatography over RP BDS Hyperprep C18 (100 Å, 8 μm; gradient elution with (0.5% NH_4OAc in water/CH_3CN 90/10)/CH_3OH/CH_3CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried (vacuum, 60 °C). Yield: 0.084 g of intermediate 26 represented by the formula



Example A16

A solution of intermediate (26) (0.0014 mol) in $SOCl_2$ (15 ml) was stirred and refluxed for 1 hour. $SOCl_2$ was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by

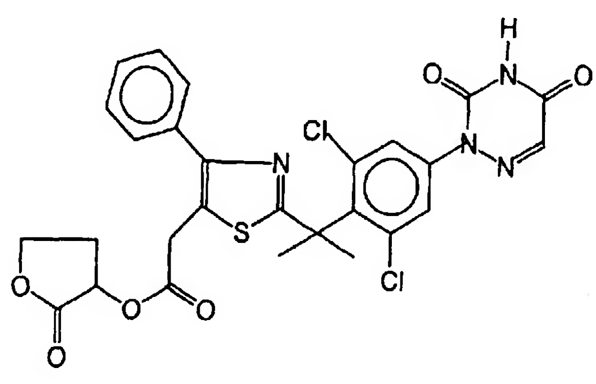
the formula



B. Preparation of the final compounds

Example B1

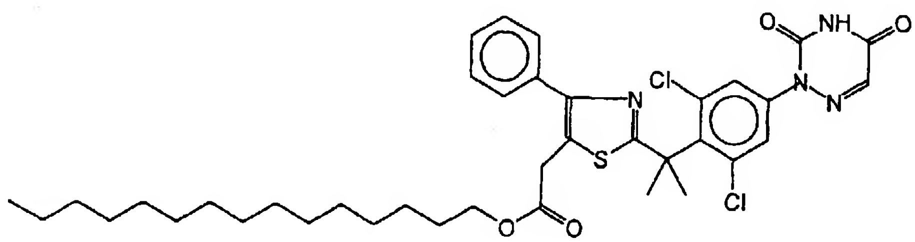
A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mol) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10)(0.00773 mol) and $NaHCO_3$ (0.0081 mol) in DMF (30ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H_2O and a saturated NaCl solution were added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.24g compound 1 having a melting point of 72°C and represented by the formula



Example B2

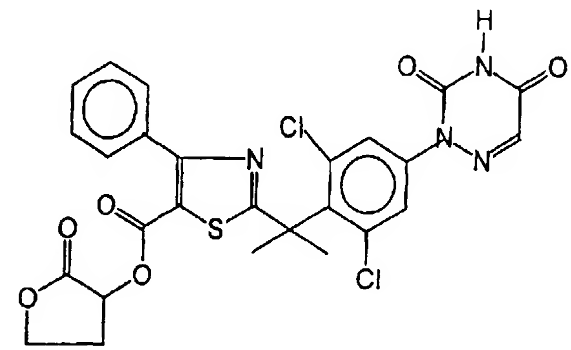
A solution of 1-bromopentadecane (0.0051 mol) in DMF (18ml) was added dropwise at

room temperature to a mixture of intermediate (10) (0.00483 mol) and $NaHCO_3$ (0.0051 mol) in DMF (10ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H_2O and NaCl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.8g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.49g compound 2 having a melting point of 80°C and represented by the formula



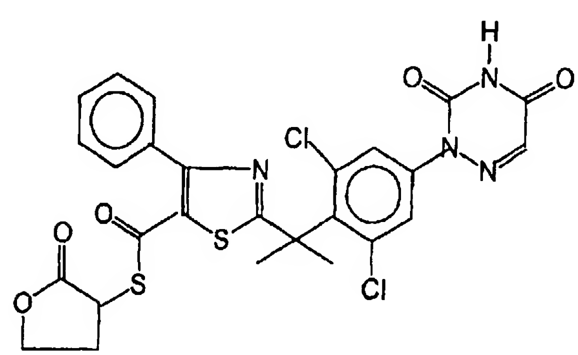
Example B3

A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mol) in DMF (12ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mol) and $NaHCO_3$ (0.0073 mol) in DMF (22ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H_2O. The precipitate was filtered off and taken up in CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.4g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 µm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH_3CN, 2-propanone and diethyl ether. The precipitate was filtered off and dried. Yielding: 0.89g compound 3 having a melting point of 208°C and represented by the formula



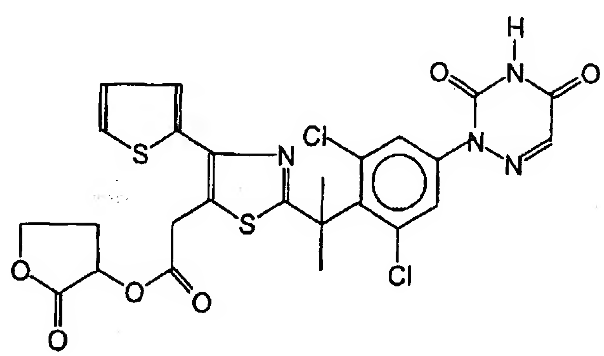
Example B4

$NaHCO_3$ (0.00835 mol) was added dropwise at 5°C under N_2 flow to a mixture of intermediate (14) (0.00795 mol) in DMF (22ml). Then a solution of 3-bromodihydro-2(3H)-furanone (0.00835 mol) in DMF (12ml) was added dropwise. The mixture was brought to RT and stirred at RT for 30 min and then poured out into H_2O and a saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was filtered off and taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.1g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. The residue was recrystallized from CH_3CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 0.85g compound 4 having a melting point of 212°C and represented by the formula



Example B5

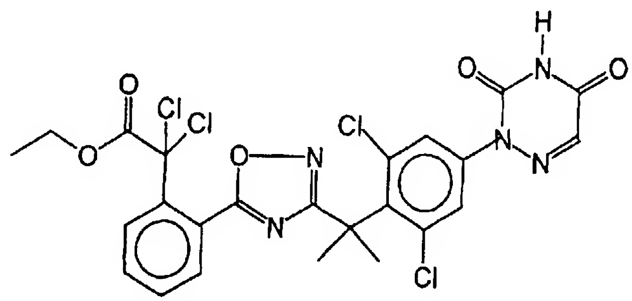
A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mol) in DMF (5ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mol) and $NaHCO_3$ (0.00172 mol) in DMF (5ml). The mixture was stirred at 70°C for 5 hours, poured out into H_2O and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH_2Cl_2/2-propanol 97/3; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 0.13g compound 5 having a melting point of 110°C and represented by the formula



Example B6

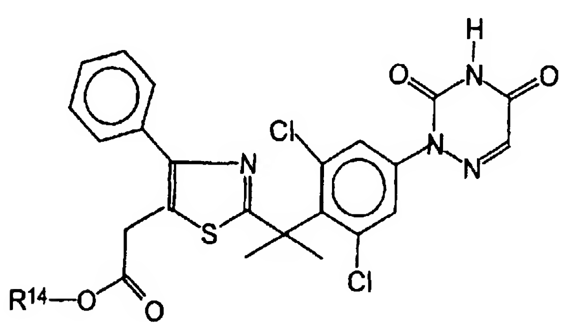
A solution of intermediate (27) (0.001 mol) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by HPLC over Hyperprep C18 (eluent: ((0.5% NH_4OAc in H_2O)/CH_3CN 90/10)/CH_3CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100) . The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and dried (vacuum, 60 °C). Yield: 0.059 g compound 6 having a melting point of 157°C and

represented by the formula



Example B7

A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH_2Cl2 and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with DIPE and dried at 50°C overnight. Yielding: 1.43g compound 7 with a molecular weight of 613.5, a melting point of 180°C and represented by the formula



IA

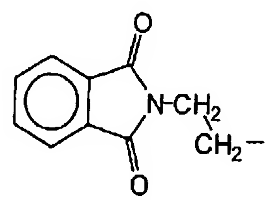
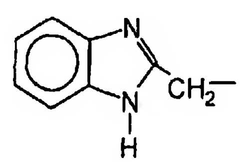
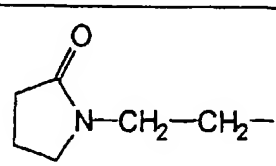
wherein R^{14} is cyclohexylmethyl.

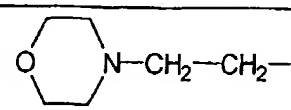
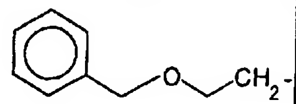
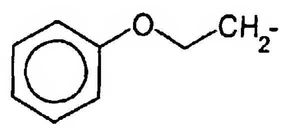
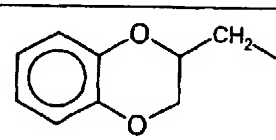
Examples B8 to B53

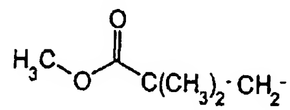
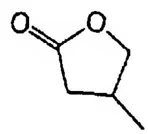
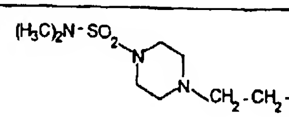
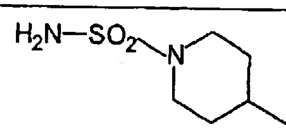
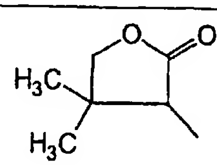
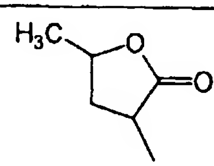
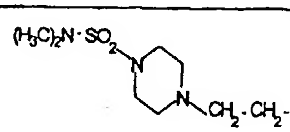
The following table 1 lists compounds of formula (IA) which were prepared according to the procedure of example B7, while replacing cyclohexylmethanol by the relevant

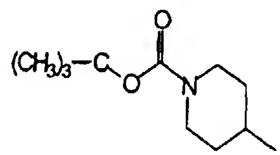
alcohol having the formula $R^{14}OH$. For the synthesis of compounds 8, 15-18, 21-23, 27, 32-34, 40-42 and 44, the amount of dichloromethane was increased up to 50 ml, and for compond 53 up to 60 ml. For the synthesis of compound 51, dichloromethane was replaced by 45 ml DMF. This table also indicates the melting point (when available) M.P.(expressed in °C) and the yield Y of obtention (expressed as a percentage) of the said compounds.

TABLE 1

COMPOUND NO.	R^{14}	M.P. (°C)	Y (%)
8			
9	Isopentyl	148	
10	2-phenyl-ethyl	130	38
11	3-phenyl-n-propyl	114	41
12	2-(N,N'-diisopropylamino)-ethyl	136	
13	2-cyano-ethyl	179	62
14			75
15	3-cyclohexyl-n-propyl	130	
16	4-phenyl-n-butyl	128	
17	Cyclopentylmethyl		
18	3-cyclopropyl-n-propyl		
19			50

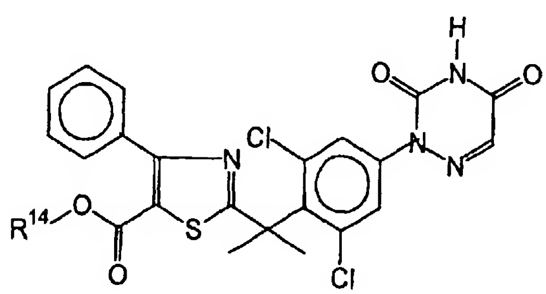
COMPOUND NUMBER	R^{14}	M.P.°C	Y(%)
20			
21	5-phenyl-n-pentyl	155	
22	Cyclobutylmethyl	150	
23	2-cyclohexylethyl	150	
24			56
25	Cyclopentylmethyl	160	
26	2-isopentenyl	175	
27	1-Cyanoethyl		
28			
29	4-Cyclohexyl-n-butyl		
30			33
31	2,2,2-trifluoroethyl		67
32	Phenylmethyl		
33	Phenyl		
34	2-methoxyethyl		
35	3-ol-n-propyl		
36	Acetamido	246	29
37	N,N'-diethylacetamido	162	60
38	Dimethylaminoethyl		
39	Styrylmethyl		
40	Cyclohexyl	183	17

COMPOUND NUMBER	R^{14}	M.P.°C	Y(%)
41	Toluylacetyloxy	151	71
42		140	37
43	N-methylpiperidinyl		28
44		160	
45			22
46	$(H_5C_2O)_2-P(=O)-CH_2-$	156	49
47		191	37
48	2,2-diethoxyethyl	156	
49			19
50	Benzylaminoethyl		
51			40
52			22

COMPOUND NUMBER	R^{14}	M.P.°C	Y(%)
53			43

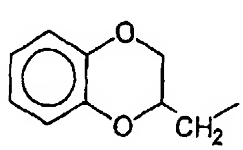
Example B 54

A mixture of 2-bromomethyl-1,4-benzodioxan (0.0044 mol) in DMF (2 ml) was added to a mixture of intermediate (13)(0.0044 mol) and $NaHCO_3$ (0.0044 mol) in DMF (8 ml). The mixture was stirred at 70°C for 6 hours, then 0.0022 mol of intermediate (13) was added. The mixture was stirred again at 70°C overnight, then poured out into H_2O, acidified with HCl (3N), extracted with EtOAc and washed with H_2O. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (3.9 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding 0.57 g compound 54 having a molecular weight of 651.5, identified in table 2 below and represented by the formula



IB

wherein R^{14} is



Example B 55

A mixture of bromo-1 phenyl -2 ethane (0.0065 mol), intermediate (13)(0.0050 mol) and $NaHCO_3$ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then poured out on ice, acidified with HCl (3N) until pH 5, extracted with EtOAc and washed with H_2O several times. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.2 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.42 g compound 55 of formula (IB), having a molecular weight of 607.5 and identified in table 2 below.

Example B 56

A mixture of phenylbromomethane (0.0065 mol), intermediate (13) (0.0050 mol) and $NaHCO_3$ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out on ice. The precipitate was filtered, washed with H_2O and the solvent evaporated. The residue was taken up in HCl (diluted) then H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.51 g compound 56 of formula (IB), having a molecular weight of 593.5 and identified in table 2 below.

Example B 57

A mixture of tert-butyl bromoacetate (0.0060 mol), intermediate (13)(0.0050 mol) and $NaHCO_3$ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with H_2O, centrifugated off and taken up in EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.0 g) was

purified by column chromatography over silica gel (eluent: CH_2Cl_2; 70-200 µm). Two fractions were collected and their solvents were evaporated. The first fraction (0.9 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.53 g compound 57 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

Example B 58

A mixture of cyclopropyl bromomethane (0.0040 mol) in DMF (10 ml) was added dropwise at RT to a mixture of intermediate (13)(0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (10 ml). The mixture was stirred at 70°C for 5 hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc. The organic layer was separated, washed several times, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.8 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 92/8; 15-40 µm; CH_3CN/NH_4Ac 1% 60/40 10µm). The pure fractions were collected and the solvent was evaporated, yielding 0.34 g compound 58 of formula (IB), having a molecular weight of 557.5 and identified in table 2 below.

Example B 59

A mixture of chloro-1 dimethylamino-2 ethane (0.0044 mol) and $NaHCO_3$ (0.0087 mol) in DMF (10 ml) was stirred at RT for 30 minutes. Intermediate (13)(0.0050 mol) was added portionwise. The mixture was stirred at 70°C overnight, cooled, poured out onto water and neutralized with HCl 3N. The precipitate was filtered, washed with H_2O and taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.4 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 94/6; 15-40 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.58 g compound 59 of formula (IB), having a molecular weight of 574.5 and identified in table 2 below.

Example B 60

A mixture of 1-chloroethyl ethylcarbonate (0.0065 mol), intermediate (13)(0.0050

mol), $NaHCO_3$ (0.0050 mol) and potassium iodide (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered off, washed with a diluted solution of HCl, washed with water, centrifugated and taken up in EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.3 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2; 70-200 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.7 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.34 g compound 60 of formula (IB), having a molecular weight of 619.5 and identified in table 2 below.

Example B 61

A mixture of ethyl bromoacetate (0.0040 mol) in DMF (2 ml) was stirred at RT. A solution of intermediate (13)(0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml) was added. The mixture was stirred at 70°C for 2 hours, cooled, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.98 g compound 61 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

Example B 62

A mixture of bromo-1 phenyl-3 propane (0.0065 mol), intermediate (13)(0.0050 mol), $NaHCO_3$ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with a diluted solution of HCl, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether/DIPE.

The precipitate was filtered off and dried, yielding 0.85 g compound 62 of formula (IB), having a molecular weight of 621.5 and identified in table 2 below.

Example B 63

A mixture of 2-(chloromethyl)benzimidazole (0.0044 mol) in DMF (5 ml) was added dropwise at RT to a mixture of intermediate (13)(0.0044 mol) and $NaHCO_3$ (0.0044 mol) in DMF (5 ml). The mixture was stirred at 70°C for 15 hours, cooled and poured out on ice. The precipitate was filtered off, washed with water several times, centrifugated off and taken up in EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.4 g compound 63 of formula (IB), having a molecular weight of 633.5 and identified in table 2 below.

Example B 64

A mixture of cyclobutyl bromomethane (0.0040 mol) in DMF (2 ml) was added at RT to a mixture of intermediate (13)(0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, then cooled, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.25/0.75; 15-40 μm, CH_3CN/NH_4Ac 75/25; 10μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.44 g compound 64 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

Example B 65

A mixture of bromo-3 propanol-1 (0.0050 mol), intermediate (13)(0.0046 mol),

$NaHCO_3$ (0.0046 mol) in DMF (10 ml) was stirred at 70°C for 6 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with a diluted solution of HCl and died. The residue was taken up in CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.6 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97.5/2.5; 15-40 µm). The desired fractions were collected and the solvent was evaporated. The residue (0.8 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.55 g compound 65 of formula (IB), having a molecular weight of 561.5 and identified in table 2 below.

Example B 66

A mixture of bromo-1 methyl-3 butene-2 (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C for 20 hours, cooled, poured out into ice water, acidified with HCl 3N and then extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.0 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5; 70-200 µm). The desired fractions were collected and the solvent was evaporated. The residue (0.5 g) was purified again by column chromatography over silica gel (eluent: CH_3CN/0.5%NH_4Oac 70/30; 10 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.25 g of compound 66 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

Example B 67

A mixture of iodomethyl trimethylacetate (0.0119 mol), intermediate (13)(0.0040 mol) and $NaHCO_3$ (0.0050 mol) in DMF (20 ml) was stirred at 70°C for 12 hours, then poured out on ice and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.3 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 µm to CH_3COONH_2/CH_3CN 25/75; 10 µm). The pure fractions were collected and the solvent

was evaporated, yielding 0.25 g compound 67 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

Example B 68

A mixture of N,N-diethyl bromoacetamide (0.0065 mol), intermediate (13) (0.0050 mol) and $NaHCO_3$ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, cooled and poured out on ice. The precipitate was filtered, washed with water, centrifugated off and taken up in EtOAc. The organic layer was separated, washed with a diluted solution of HCl, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.4 g) was crystallized from CH_3CN and diethylether. The precipitate was filtered off and dried, yielding 0.7 g compound 68 of formula (IB), having a molecular weight of 616.5 and identified in table 2 below.

Example B 69

A mixture of 4-chloro-1,3-dioxolan-2-one (0.0031 mol), intermediate (13) (0.0024 mol), $NaHCO_3$ (0.0024 mol) and potassium iodide (0.0024 mol) in DMF (6 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.65 g compound 69 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

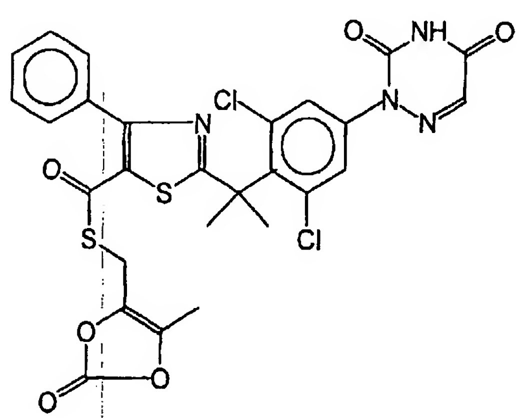
Example B 70

A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0034 mol), intermediate (13)(0.0026 mol), $NaHCO_3$ (0.0026 mol) in DMF (6 ml) was stirred at 70°C for 12 hours, then poured out into ice water and acidified with HCl 3N. The precipitate was

filtered, washed with water and taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm) then over Kromasil (eluent: CH_3CN/CH_3OH 80/20; 3.5 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.28 g of compound 70 of formula (IB), having a molecular weight of 615.5 and identified in table 2 below.

Example B 71

A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0046 mol), intermediate (14)(0.0035 mol), $NaHCO_3$ (0.0035 mol) in DMF (10 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH_2Cl_2. The organic layer was separated, dried (MgSO4), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm) then over Kromasil (eluent: $CH_3CN/AcNH_4$ 65/35; 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.36 g (33%) of compound 71, having a molecular weight of 631.5 and a melting point of 97°C and represented by the formula:



Example B 72

4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0081 mol) was dissolved in DMF (20 ml). This solution was added dropwise to intermediate (10)(0.0077 mol) and $NaHCO_3$ (0.0081 mol) in DMF (30 ml) under nitrogen atmosphere. The reaction mixture was

stirred at 50°C for 3 hours, poured out into water (+ NaCl) and extracted three times with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by high performance liquid chromatography over silica gel (eluent: CH_2Cl_2/CH_3CN). The desired fractions were collected and the solvent was evaporated, yielding 0.86 g of an oily fraction which was stirred in hexane/EtOAc (1:1) until a white precipitate was formed. This precipitate was filtered off, washed with DIPE and dried overnight, yielding 0.58 g of compound 72, having a molecular weight of 629.5 and a melting point of 149°C and represented by the formula:

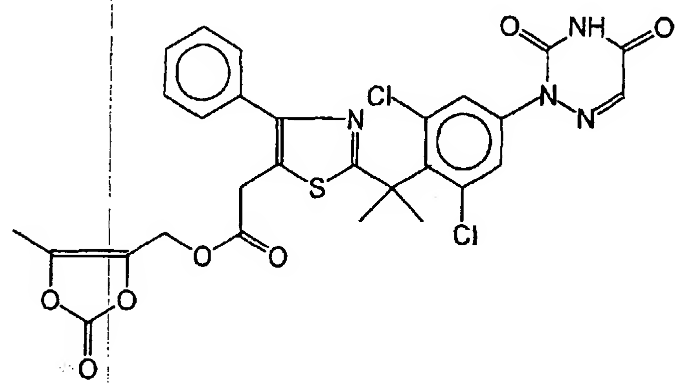
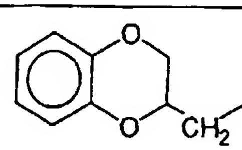
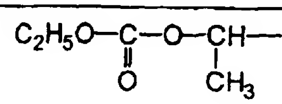
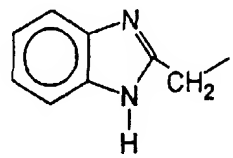
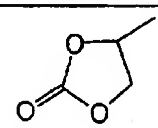
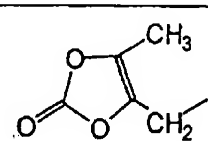


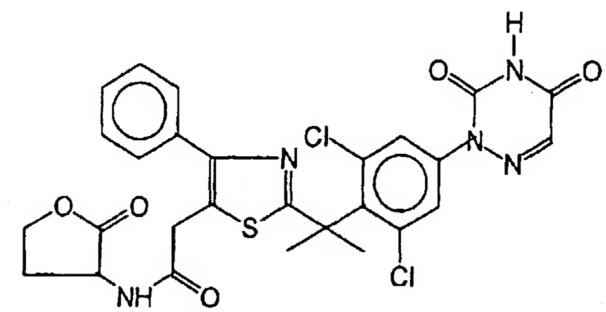
TABLE 2

COMPOUND NO.	R^{14}	M.P. (°C)	Y (%)
54		182	53
55	Phenyl-2 ethyl	146	20
56	Phenylmethyl	167	30
57	Tert-butyl acetyl	165	17
58	Cyclopropylmethyl	100	13
59	dimethylaminoethyl	204	22
60		163	11

COMPOUND NUMBER	R^{14}	M.P.°C	Y(%)
61	ethylacetyl	198	
62	Phenyl-3 propyl	165	27
63		172	14
64	cyclobutylmethyl	80	33
65	Hydroxy-3 propyl	85	31
66	Methyl-3-butene-2-yl	90	11
67	trimethylacetyl	80	10
68	diethylacetamido	157	
69		90	36
70		102	14

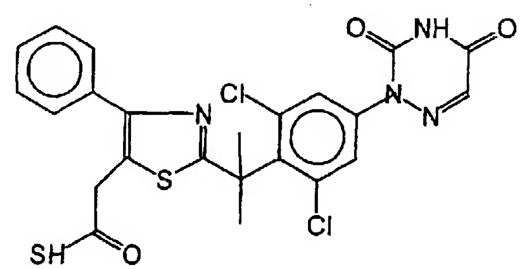
Example B 73

A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH_2Cl_2 and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was filtered over silica gel (eluent: CH_2Cl_2/EtOAc 50/50). The product fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The residue was stirred in DIPE, filtered off, washed and dried at 50°C under vacuum for two days, yielding 1.43g (62%) compound 73 having a molecular weight of 600.5 and represented by the formula

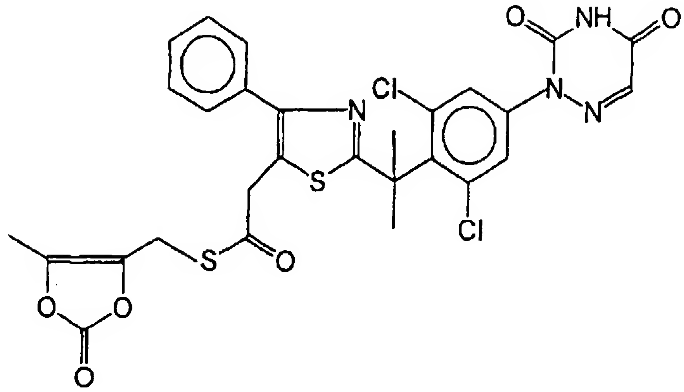


Examples B 74 and B 75

A mixture of intermediate (10)(0.0156 mol) and 1,1'-carbonylbis-1H-imidazole (0.0232 mol) in DMF(160ml) was stirred at RT for 3 hours, and then treated with an excess of hydrogen sulfide for 20 minutes at RT, then with nitrogen overnight. Half of this reaction mixture, containing 0.0078 mol of compound 74 represented by the formula

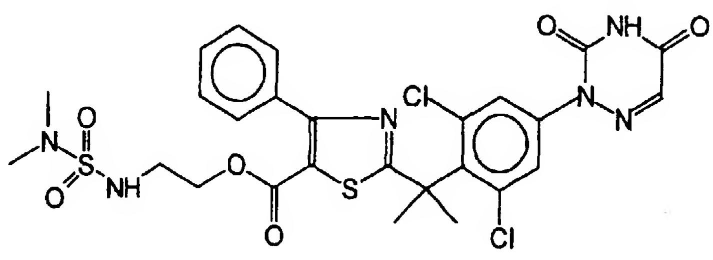


in 80 ml DMF, was treated with a solution of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.013 mol) in DMF (20 ml). The reaction mixture was stirred for one hour, then poured out into water and extracted twice with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/EtOAc 92.5/7.5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried under vacuum for one hour, yielding 2.68 g (54%) compound 75 represented by the formula



Example B 76

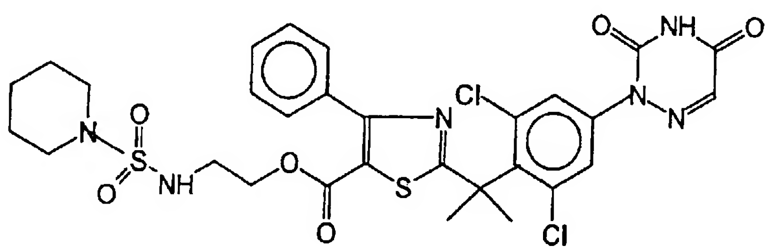
1,1'-carbonylbis-1H-imidazole (0.0017 mol) was added to a mixture of intermediate (13) (0.0014 mol) in DMF (6 ml). The mixture was stirred at 40°C for one hour. A solution of N,N-dimethyl ethanolaminesulfonamide (0.0028 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0014 mol) in DMF (3 ml) was added. The mixture was stirred at 40°C for 3 hours, then brought to RT, poured out into water, acidified with HCl 3N, filtered and washed with water. The precipitate was filtered off and dried. The residue was taken up in diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/CH_3CN/DIPE, yielding 0.77 g (65%) of compound 76 having a molecular weight of 653.5 g, a melting point of 150°C and being represented by the formula



Example B 77

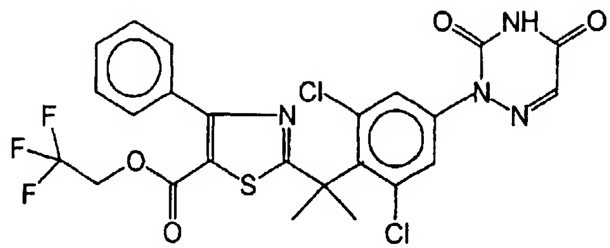
1,1'-carbonylbis-1H-imidazole (0.0013 mol) was added at RT to a mixture of

intermediate (13) (0.0010 mol) in DMF (4 ml). The mixture was stirred at 40°C for 45 minutes. A mixture of N-(2-hydroxyethyl)-1-piperidinesulfonamide (0.0019 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0010 mol) in DMF (2 ml) was added fastly. The mixture was stirred at 40°C for 90 minutes, then brought to RT, poured out into water and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH_2Cl_2, then filtered and dried again and then purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.34 g) was taken up in DIPE. The precipitate was filtered off and dried, yielding 0.18 g (57%) of compound 77 having a molecular weight of 693.5 g, a melting point of 126°C and being represented by the formula



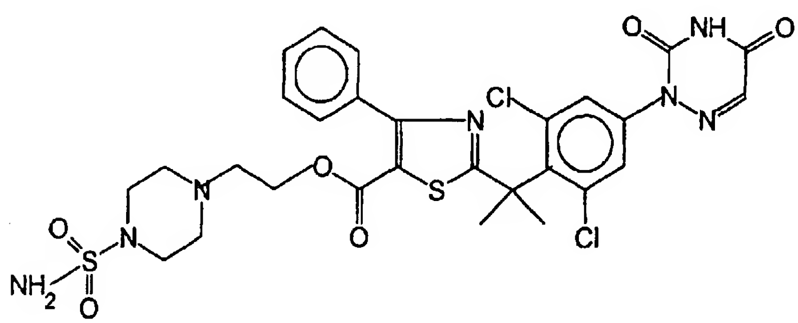
Example B 78

1,1'-carbonylbis-1H-imidazole (0.0030 mol) was added at RT to a mixture of intermediate (13) (0.0024 mol) in DMF (12 ml). The mixture was stirred at 40°C for one hour. A solution of 2,2,2-trifluoroethanol (0.0048 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0024 mol) in DMF (5 ml) was added. The mixture was stirred at 40°C for 2 hours, poured out on ice/HCl 3N, filtered and washed with water. The precipitate was taken up in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether, then filtered off and dried, yielding 0.51 g (31%) of compound 78 having a molecular weight of 583.5 g, a melting point of 180°C and being represented by the formula



Example B 79

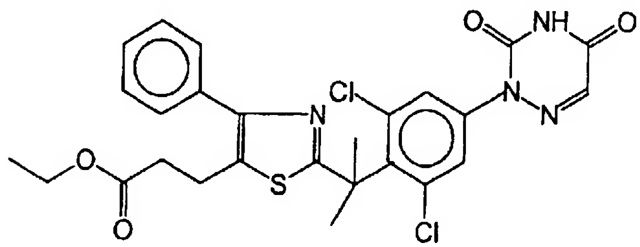
1,1'-carbonylbis-1H-imidazole (0.0050 mol) was added to a mixture of intermediate (13) (0.0040 mol) in DMF (15 ml). The mixture was stirred at 40°C for one hour. A solution of N-(2-hydroxyethyl)-N'-piperazinesulfonamide (0.0104 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0040 mol) in DMF (10 ml) was added. The mixture was stirred at 40°C for 2 hours, then brought to RT, poured out on ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH_2Cl_2/CH_3OH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.7 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 96/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.3 g (10%) of compound 79 having a molecular weight of 694.5 g, a melting point of 133°C and being represented by the formula



Example 80

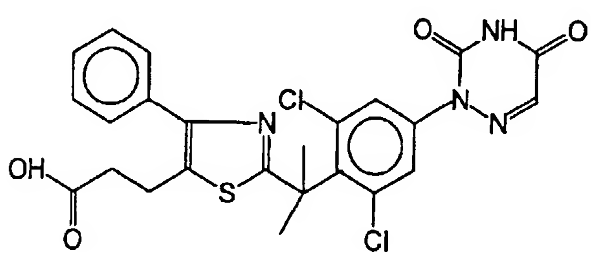
A mixture of intermediate (8) (0.0097 mol) and γ-bromo-δ-oxo-benzenepentanoic acid ethyl ester (0.0126 mol) in ethanol (150 ml) was stirred and refluxed overnight. The solvent was evaporated and the residue was taken up in methylene chloride. The organic

layer was separated, washed with a 10% solution of K_2CO_3 then with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.7 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 3.2 g (59 %) of compound 80 having a molecular weight of 559.5 g, a melting point of 155°C and being represented by the formula



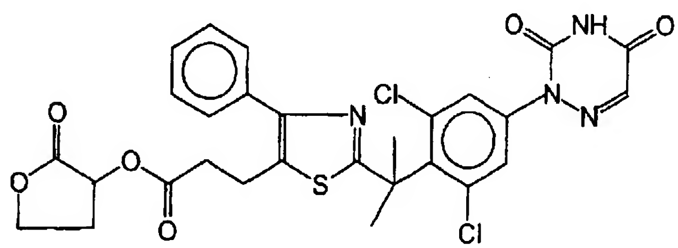
Example 81

A mixture of compound 80 (0.0032 mol) and sodium hydroxide (0.0096 mol) in methanol (20 ml) and THF (20 ml) was stirred at RT for 12 hours, poured out on ice, acidified with HCl 1N and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 1.7 g of a compound of the formula



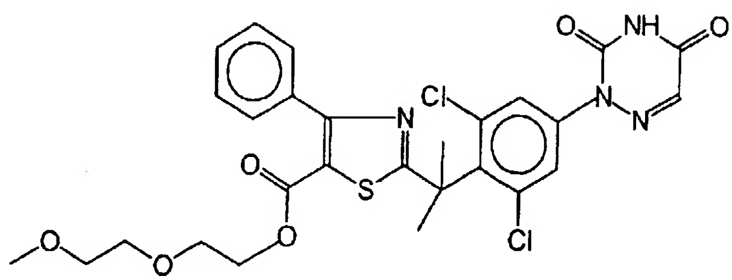
which, after crystallization from diethyl ether, shows a melting point of 186°C. A mixture of α-bromo-γ-butyrolactone (0.0021 mol) in DMF (5 ml) was added dropwise at RT to a mixture of the compound obtained in the preceding step (0.0021 mol) and $NaHCO_3$ (0.0021 mol) in DMF (5 ml). The mixture was stirred at 70°C for 5 hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc and

washed with H_2O. The organic layer was separated, washed several times with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether and CH_3CN. The precipitate was filtered off and dried, yielding 0.25 g (19%) of compound 81 having a molecular weight of 615.5 g, a melting point of 190°C and being represented by the formula



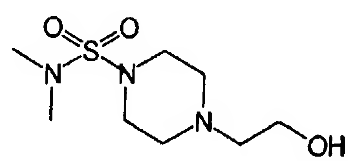
Example B 82

Intermediate (13) (0.0050 mol) was added to DMF (20 ml) under nitrogen flow. 1,1'-carbonylbis-1H-imidazole (0.0062 mol) was added and the mixture was stirred at 40°C for one hour. Then 2-(2-methoxyethoxy) ethanol (0.0099 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0050 mol) were added and the resulting mixture was stirred at 40°C for 12 hours, cooled and then diluted with diethyl ether. The organic layer was separated, washed with HCl 3N then with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.5 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.03 g (34%) of compound 82 having a molecular weight of 605.5 g, a melting point of 151°C and being represented by the formula



Example B 83

A mixture of N,N-dimethyl-1-piperazinesulfonamide (0.0423 mol) in methanol (100 ml) and methylene chloride (30 ml) was treated with an excess of gaseous ethylene oxide at 5°C for 90 minutes. The reaction mixture was stirred at RT for 3 hours. The solvent was evaporated, then co-evaporated with toluene. The residue was stirred overnight in 7N NH_3 /CH_3OH and the solvent was evaporated, then co-evaporated with toluene. The residue (10.3 g) was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 92.5/7.5). The desired fractions were collected and the solvent was evaporated, then co-evaporated with toluene, yielding 6.9 g (69 %) of a compound 83 represented by the formula

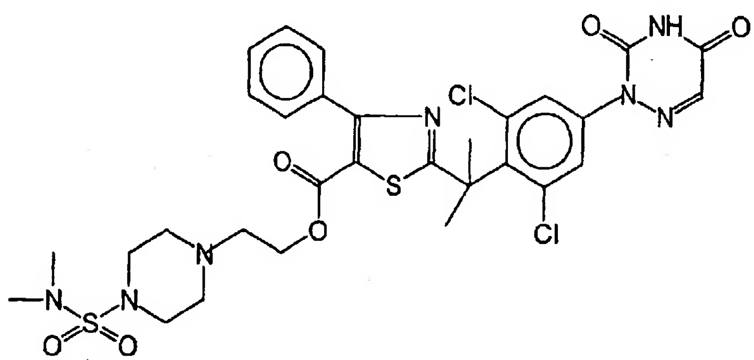


which after crystallization from diethyl ether, shows a melting point of 186°C.

Example B 84

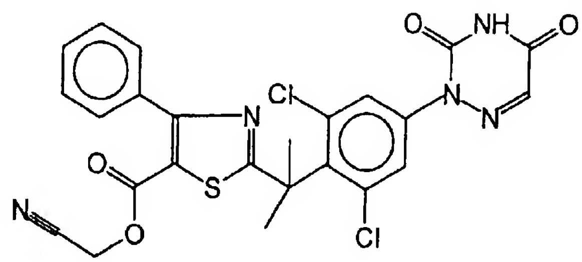
Intermediate (13) (0.0036 mol) was added to DMF (15 ml) under nitrogen flow. 1,1'-carbonylbis-1H-imidazole (0.0045 mol) was added and the mixture was stirred at 40°C for one hour. Then a solution of compound 83 (0.0072 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0036 mol) was added over two minutes and the resulting mixture was stirred at 40°C for 5 hours, brought to RT, poured out into water, filtered and taken

up in CH_2Cl_2. The organic layer was separated, washed with water, dried (MgSO4), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (1.3 g) was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried, yielding 1.0 g of compound 84 having a molecular weight of 722.7 g, a melting point of 220°C and being represented by the formula



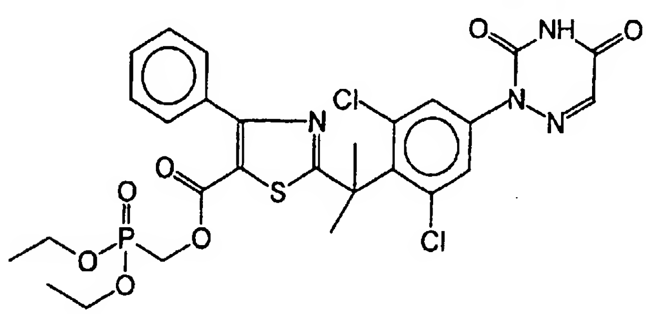
Example B 85

A mixture of bromoacetonitrile (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, cooled, poured out into ice water, acidified with HCl (3N) and then extracted with EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.9 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.25/0.75; 15-40 µm). The fractions were collected and, after evaporation of their solvent, purified again by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.25/0.75; 15-40 µm). The pure fractions were collected and the solvent evaporated, yielding 0.26 g (12%) of compound 85 having a molecular weight of 542.5 g and being represented by the formula



Example B 86

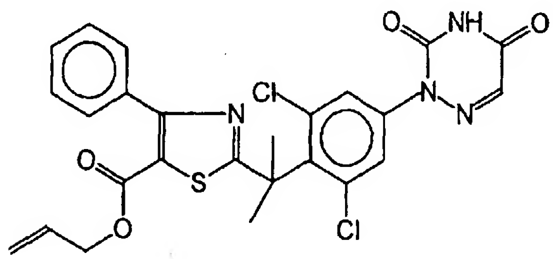
Intermediate (13) (0.0034 mol) was added under nitrogen flow to DMF (25 ml). 1,1'-carbonylbis-1H-imidazole 0.0043 mol) was added and the mixture was stirred at 40°C for one hour. (Hydroxymethyl) phosphonate diethyl ester (0.0068 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0034 mol) were added and the mixture was stirred at 40°C for 5 hours, then brought to room temperature, poured out into water and acidified with HCL 3N. The precipitate was filtered off and taken up in methylene chloride. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The fractions were collected and the solvent was evaporated. The residue (1.4 g) was taken up in DIPE. The precipitate was filtered off and dried, yielding 1.3 g of compound 86 having a molecular weight of 653.5 g, a melting point of 88°C and being represented by the formula



Example B 87

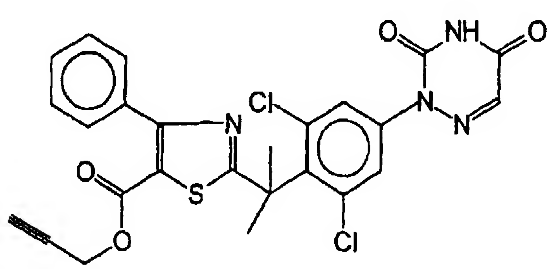
A mixture of bromo-3 propylene-1 (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, poured out into ice water and extracted with

EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5; 35-70 µm). The fractions were collected and the solvent evaporated. The residue (0.8 g) was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.31 g (15%) of compound 87 having a molecular weight of 543.5 g, a melting point of 172°C and being represented by the formula



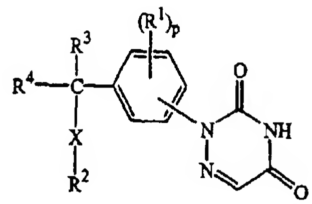
Example B 88

A mixture of bromoacetylene (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and $NaHCO_3$ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2; column: 70-200 µm). The desired fractions were collected and the solvent evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH_3CN/NH_4Oac 68/32; column Kromasil C18 10 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.41 g of compound 88 having a molecular weight of 541.5 g, a melting point of 180°C and being represented by the formula



Claims

1. A compound having the formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or-X-R^2 taken together may represent cyano;

Y represents O, S, NR^5, or $S(O)_2$;

each R^1 independently represents C(=0)·Z-R^{14}, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with C(=0)-Z·R^{14}, Het^3, R^6 or NR^7R^8;

R^2 represents Het^1, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkyl or C_{1-6}alkyl substituted with one or two substituents selected from C(=0)·Z-R^{14}, hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy optionally substituted with C(=0)-Z-R^{14}, C_{1-6}alkylsulfonyloxy, C_{3-7}cycloalkyl optionally substituted with C(=0)-Z-R^{14}, aryl, aryloxy, arylthio, Het^1, Het^1oxy and Het^1thio; and if X is O, S or NR^5, then R^2 may also represent aminothiocarbonyl, C_{1-4}alkylcarbonyl optionally substituted with C(=0)-Z-R^{14}, C_{1-4}alkylthiocarbonyl optionally substituted with C(=0)-Z-R^{14} , arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl;

R^3 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl;

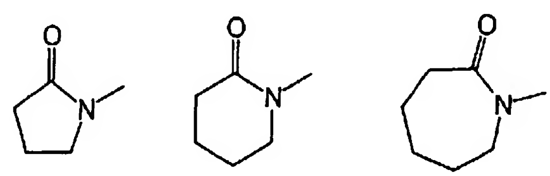
R^4 represents hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6}alkanediyl;

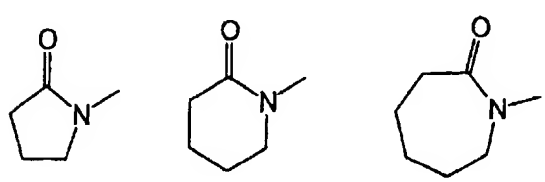
R^5 represents hydrogen or C_{1-4}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, piperidinylsulfonyl, mono- or di(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, arylcarbonyl, Het^{3}carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^{3}aminocarbonyl, Het^{3}aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C1-4alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6; or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a radical of formula



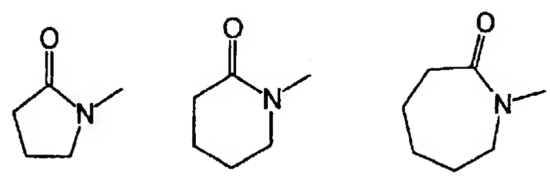
R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, Het^{3}carbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^{3}aminocarbonyl, Het^{3}aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C1-4alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, Het^3, Het^4 and R^6; or R^9 and R^{10} taken together with the nitrogen atom to which they are attached form a radical of formula



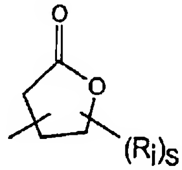
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy optionally substituted with C(=0)-Z-R^{14}, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)$NR^{15}R^{16}$, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl optionally

substituted with C(=O)-Z-R^{14}, C_{3-7}cycloalkyloxy optionally substituted with C(=O)-Z-R^{14}, phthalimide-2-yl, Het^3 and C(=O)Het^3;

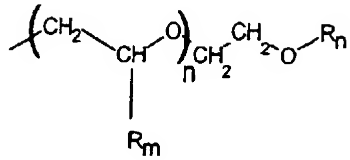
R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-R^{14}, -C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} and R^6; or R^{12} and R^{13} taken together with the nitrogen atom to which they are attached form a radical of formula



each R^{14} independently represents hydrogen, C_{1-20}acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20}alkyl, C_{3-20}alkenyl optionally substituted with phenyl, C_{3-20}alkynyl, C_{3-7} cycloalkyl, polyhaloC_{1-20}alkyl, Het^5, phenyl or C_{1-20} alkyl substituted with one or more substituents selected from hydroxy, $NR^{17}R^{18}$, phenyl, mono- or di-(C_{1-4}alkyl)amino, cyano, Het^5, C_{1-4} alkyloxycarbonyl, phenyl C_{1-4} alkyloxycarbonyl and C_{3-7} cycloalkyl, or R^{14} represents a radical of formula



(a)



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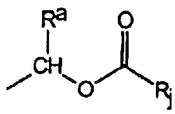
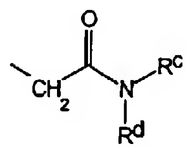
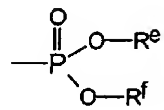


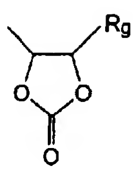
(c)



(d)



(e)



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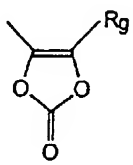
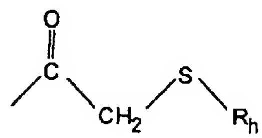
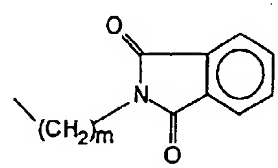


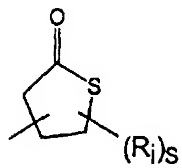
(i)



(j)



(k)



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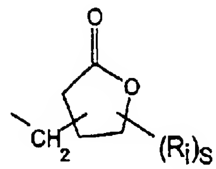
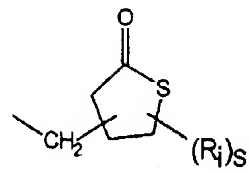
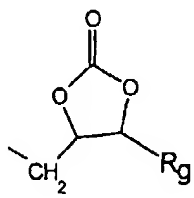


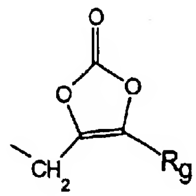
(m)



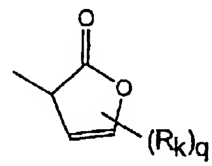
(n)



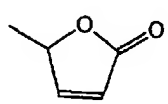
(o)



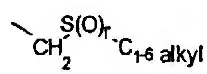
(p)



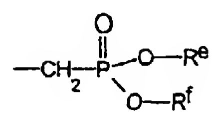
(q)



(r)



(s)



(t)

wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;

R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C_{1-6}alkyl, phenyl or C_{3-7}cycloalkyl; or

R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;

R_g, R_h and R_k are each independently hydrogen or C_{1-4} alkyl;

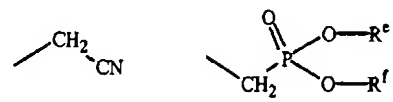
R_i is C_{1-4}alkyl;

R_j is $-O-R_b$, C_{1-6}alkyl, phenyl or C_{3-7}cycloalkyl optionally substituted with C_{1-4} alkyloxy;

where R_m is hydrogen or C_{1-4} alkyloxy and R_n is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, phenyl or phenylC_{1-4}alkyl

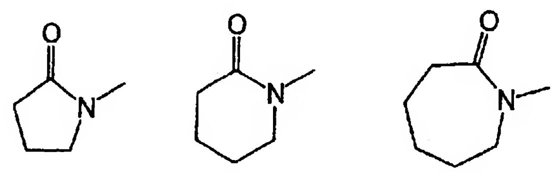
each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group; or

$-Z-R^{14}$ taken together form a radical of formula



(f) (g)

R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, $-C(=O)-Z-R^{14}$, arylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, aminocarbonylmethylene, mono- or di(C_{1-4}alkyl) aminocarbonylmethylene, Het^3aminocarbonyl, Het^3aminothiocarbonyl, pyridinylC_{1-4}alkyl, Het^3 or R^6; or R^{15} and R^{16} taken together with the nitrogen atom to which they are attached form a radical of formula



R^{17} and R^{18} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl, -C(=O)-Z-C_{1-6}alkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl and R^6;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, $C(=O)-Z-R^{14}$, R^6, $-O-R^6$, phenyl, Het^3, $C(=O)Het^3$ and C_{1-4}alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C_{1-4}alkyloxy, $C(=O)-Z-R^{14}$, -Y-C_{1-4}alkanediyl-$C(=O)-Z-R^{14}$, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^4, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^4 and R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-Z-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

Het^5 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{17}R^{18}$, C(=O)-Z-C_{1-6}alkyl, R^6, sulfonamido and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-Z-C_{1-6}alkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-C_{1-6}alkyl, R^6 and $NR^{17}R^{18}$;

provided however that

- R^2 is other than C_{1-6} alkyloxycarbonylC_{1-6}alkyl or aminocarbonyl; and
- R^7, R^8, R^9 and R^{10} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, C(=O)-O-R^{19}, C_{1-4}alkanediylC(=O)-O-R^{19} or –Y-C_{1-4}alkanediylC(=O)-O-R^{19}; and
- R^{12} and R^{13} are other than C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkylcarbonylcarbonyl; and
- R^{11} is other than C(=O)-O-R^{19}, Y-C_{1-4}alkanediyl – C(=O)-OR^{19}, C(=O)NH_2, C(=O)NHC_{1-4}alkyl or C(=O)NHC_{3-7}cycloalkyl; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkylcarbonyl, hydroxy C_{1-4}alkylcarbonyl or C_{1-4}alkyloxycarbonylcarbonyl; and
- aryl is other than phenyl substituted with C(=O)-O-R^{19}, C(=O)NH_2, C(=O)NHC_{1-4}alkyl, C(=O)NHC_{3-7}cycloalkyl and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{19} or Y-C_{1-4}alkanediyl – C(=O)-O-R^{14}; and
- Het^3 is other than a monocyclic heterocycle substituted with C(=O)-O-R^{19} and/or with C_{1-4}alkyl substituted with C(=O)-O-R^{19} and/or Y-C_{1-4}alkanediyl – (=O)-O-R^{19}; and

- in each of the above proviso's R^{19} is defined as hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene or mono- or di(C_{1-4}alkyl)aminocarbonylmethylene; and
- the said compound of formula (I) contains at least one – C(=O)-Z-R^{14} moiety.

2. A compound according to claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R^2, R^3 and R^4 substituents.

3. A compound according to claims 1 or 2 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}.

4. A compound according to any of claims 1 to 3 wherein R^3 and R^4 are both methyl and -X-R^2 is Het^1.

5. A compound according to any of claims 1 to 4 wherein p is 1 or 2 and each R^1 is chloro.

6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any of claims 1 to 5.

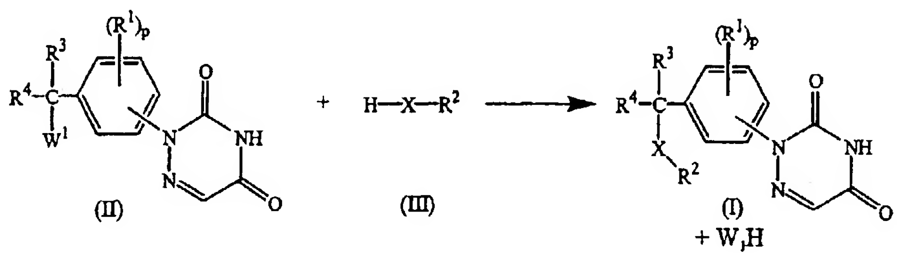
7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to any of claims 1 to 5.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

9. Use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

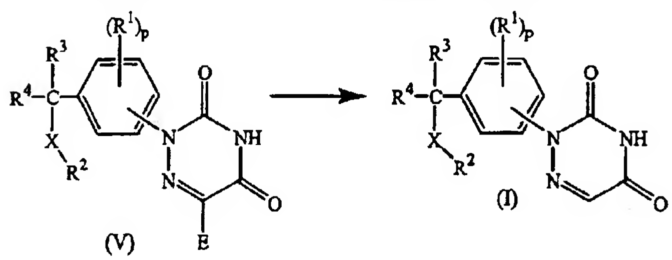
10. A process for preparing a compound as claimed in claim 1, comprising the step of

a) reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;



wherein R^1 R^2, R^3, R^4, p and X are as defined in claim 1 or;

b) eliminating the group E of a triazinedione of formula (V)



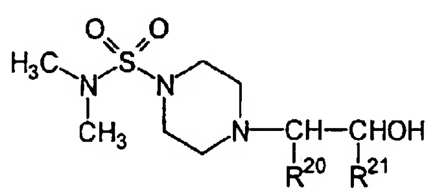
wherein E is an appropriate electron attracting group and R^1, R^2, R^3, R^4, X and p are as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of
   a) radiolabelling a compound as defined in claim 1;
   b) administering said radiolabelled compound to biological material,
   c) detecting the emissions from the radiolabelled compound.

12. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

13. A compound of formula



(XXIII)

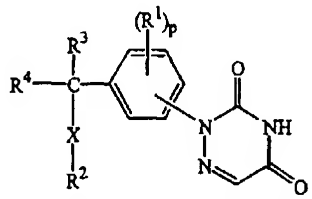
wherein R^{20} and R^{21} are each independently selected from hydrogen or C_{1-20} alkyl or R^{20} and R^{21} taken together with the carbon atom to which they are attached form a cycloalkyl radical.

14. Use of the compound of claim 13 for preparing a compound of claim 1 wherein Het^5 represents a sulfonamido substituted piperazine.

ABSTRACT

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein p is 0 to 4; X is O, S, NR^5 or a direct bond; Y is O, S, NR^5 or $S(O)_2$; R^1 independently is C (=O)-Z-R^{14} ,C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or substituted C_{1-4}alkyl; R^2 is Het^1, optionally substituted C_{3-7}cycloalkyl or C_{1-6}alkyl and if X is O, S or NR^5, then R^2 may also represent C(=O)-Z-R^{14}, aminothiocarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het^1carbonyl or Het^1thiocarbonyl; R^3 and R^4 independently are hydrogen, C_{1-6}alkyl or C_{3-7}cycloalkyl or R^3 and R^4 together form a C_{2-6}alkanediyl; R^5 is hydrogen or C_{1-4}alkyl; R^7 and R^8 are independently hydrogen, optionally substituted C_{1-4}alkyl, aryl, a carbonyl containing moiety, C_{3-7}cycloalkyl, -Y-C_{1-4}alkanediyl-C(=O)-Z-R^{14} or Het^3; R^6 is a sulphonyl; R^{14} is hydrogen, C_{1-20}alkyl, C_{3-7}cycloalkyl, C_{1-20} acyl or another radical; Z is O, S, NH, -CH_2O- or -CH_2S- whereby -CH_2- is attached to the carbonyl group; aryl is optionally substituted phenyl; Het^1, Het^2, Het^3 and Het^4 are optionally substituted heterocycles, provided that the said compounds contain at least one -C(=O)-Z-R_{14} moiety; to processes for their preparation and pharmaceutical compositions comprising them. It further relates to their use as a medicine.